

Impact of Carotid Arterial Narrowing on Outcomes of Patients With Acute Coronary Syndromes

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The present prospective observational study was conducted in 323 consecutive patients with acute coronary syndrome, 101 (31%) of whom were diagnosed with carotid arterial narrowing by ultrasonography. At follow-up, patients with carotid disease had a greater incidence of cardiovascular events than did those with normal carotid arteries. Outcomes of patients with concomitant carotid disease who underwent cardiac revascularization were similar to those who received conservative treatment. ©2004 by Excerpta Medica, Inc.

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A recent study in patients with acute coronary syndrome (ACS) has reported that the presence of prior cerebrovascular accidents, transient ischemic attacks, or peripheral arterial disease is predictive of increased hazards of death, reinfarction, recurrent ischemia, and stroke. However, despite increased severity of coronary artery disease (CAD) and greater incidence of hypercholesterolemia, patients with carotid arterial disease were treated less aggressively than were patients without carotid disease, which may partly explain their worse outcomes.¹ Moreover, the relation of these events to different treatment strategies has not been studied. Accordingly, we evaluated the prognostic effect of carotid disease in relation to treatment strategy in patients with ACS.

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The initial study population consisted of 323 consecutive patients admitted to our coronary care unit between January 2000 and December 2001 due to ACS diagnosed according to current guidelines by the American College of Cardiology and the American Heart Association.² Concomitant uncontrolled hypertension was diagnosed when blood pressure was not maintained at <140/90 mm Hg, which occurred because hypertension was refractory to treatment or the patient was noncompliant. Patients with significant valvular disease were excluded. Within 15 days of admission, all patients underwent coronary angiography and ultrasonographic assessment of carotid arteries. According to the decision of the treating physicians, who were unaware of the study goals, patients

were managed conservatively or underwent coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention).

Patients were followed prospectively for a median of 19 months (first quartile 12 months, third quartile 24 months).

Coronary angiography was performed according to standard femoral or brachial techniques. Several views of each coronary artery were analyzed. The severity of arterial stenoses, defined as the maximal percent reduction in luminal diameter, was determined according to the caliper technique.³ Significant coronary stenosis was defined as $\geq 70\%$ lumen narrowing in any of the 3 coronary arteries or their main branches or $\geq 50\%$ lumen narrowing of the left main coronary artery. The extent of CAD was classified as 1-, 2- or 3-vessel CAD according to the number of major coronary arteries with significant stenosis. Significant left main artery stenosis was scored as 2-vessel disease.^{4,5}

Ultrasonographic examinations were performed with a Sonos 5500 (Hewlett-Packard, Palo Alto, California). B-mode examination of carotid arteries was performed with a 7.5-MHz linear array transducer. Plaques were identified as focal widenings of the vessel wall $>50\%$ relative to adjacent segments, with protrusion into the lumen, composed of calcified or noncalcified components.⁶ The degree of stenosis was established according to standard imaging and Doppler ultrasonographic criteria.⁷ Two-dimensional echocardiography was performed according to standard protocol. Left ventricular ejection fraction was measured by Simpson's method.

Follow-up data were collected after a review of the patient's hospital chart, contact with the patient's physician, telephone interview with the patient, and the patient's visits to an outpatient clinic. Medications during follow-up were recorded. Target events were death, nonfatal myocardial infarction, and recurrent angina requiring hospitalization. Death was defined as cardiac if strictly related to proven cardiac causes (fatal myocardial infarction, acute heart failure, or malignant arrhythmias). Sudden death, defined as unexpected death, occurring outside the hospital, and preceded by no apparent symptoms or by symptoms <1 hour in duration, was classified as cardiac in origin. Myocardial infarction was diagnosed on the basis of documented electrocardiographic changes and typical cardiac enzyme release (troponin I and creatine phosphokinase-MB mass).⁸ Angina requiring hospitalization was diagnosed on the basis of typical chest pain. Revascularization was considered in patients with favorable anatomy and/or positive results from stress testing. Cardiac death and nonfatal myocardial

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TABLE 1 Baseline Characteristics				
Variable	All Patients (n = 323)	Carotid Disease		p Value
		+(n = 101)	0 (n = 222)	
Age >75 yrs	21 (6%)	11 (11%)	20 (9%)	NS
Women	76 (24%)	18 (18%)	58 (26%)	NS
Follow-up (mo)	17 ± 8	16 ± 8	17 ± 7	NS
Ejection fraction (%)	53 ± 11	52 ± 8	54 ± 11	NS
Controlled hypertension	206 (64%)	65 (64%)	141 (64%)	NS
Uncontrolled hypertension	47 (15%)	23 (23%)	24 (11%)	0.004
History of myocardial infarction	48 (15%)	20 (20%)	28 (13%)	0.09
Smoking	27 (8%)	5 (5%)	22 (10%)	NS
Type 2 diabetes mellitus	58 (18%)	30 (30%)	28 (13%)	0.0002
Previous revascularization	16 (5%)	7 (7%)	9 (4%)	NS
Total cholesterol (mg/dl)	202 ± 44	203 ± 45	201 ± 44	NS
LDL cholesterol (mg/dl)	126 ± 37	130 ± 39	125 ± 37	NS
Triglycerides (mg/dl)	128 ± 72	126 ± 68	129 ± 74	NS
Diagnosis at admission				
ST-elevation AMI (%)	72 (22%)	20 (20%)	52 (23%)	NS
Non-ST-elevation AMI (%)	55 (17%)	20 (20%)	35 (16%)	NS
Unstable angina pectoris	196 (61%)	61 (60%)	135 (61%)	NS
No. of narrowed coronary arteries				
1	101 (31%)	19 (19%)	82 (37%)	0.001
2	75 (23%)	32 (32%)	43 (19%)	0.02
3	100 (31%)	45 (45%)	55 (25%)	0.0004

AMI = acute myocardial infarction; LDL = low-density lipoprotein.

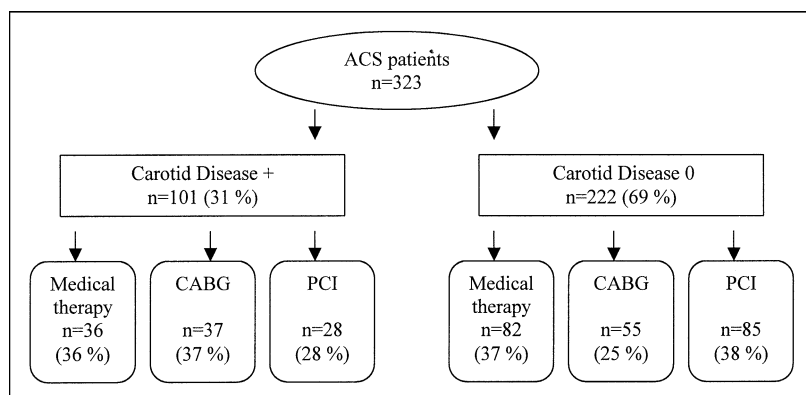


FIGURE 1. Distribution of patients according to presence or absence of carotid disease and treatment strategy. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

TABLE 2 Outcomes During Follow-up				
Cardiovascular Events	All Patients	Carotid Disease		p Value
		+	0	
All treatment strategies				
Cardiac death	11 (3%)	8 (8%)	3 (1%)	0.001
Nonfatal myocardial infarction	14 (4%)	8 (8%)	6 (3%)	0.03
Recurrent angina leading to hospitalization	46 (14%)	24 (24%)	22 (9%)	0.009
Conservative treatment				
Cardiac death	6 (5%)	5 (14%)	1 (1%)	0.005
Nonfatal myocardial infarction	7 (6%)	2 (6%)	5 (6%)	NS
Recurrent angina leading to hospitalization	16 (14%)	9 (25%)	7 (9%)	0.02
Revascularization				
Cardiac death	5 (2%)	3 (5%)	2 (1%)	NS
Nonfatal myocardial infarction	7 (3%)	6 (9%)	1 (0.7%)	0.002
Recurrent angina leading to hospitalization	30 (15%)	15 (23%)	15 (11%)	0.02

infarction were defined as hard events. Only the worst event was used in statistical analysis to avoid overlap.

Statistical analysis was performed with SPSS 11.0.1 (SPSS, Inc., Chicago, Illinois). Mean data are presented as mean ± SD unless otherwise noted. Differences between patients with carotid disease and patients without carotid disease were assessed by unpaired *t* test and chi-square test, as appropriate. Kaplan-Meier survival analysis was performed for the 2 groups, and differences were assessed by the log-rank test. To find independent predictors of outcomes, Cox's multivariate regression analysis was performed using a forward stepwise procedure and a 5% entry level. The variables considered in the models were age, gender, history of myocardial infarction, left ventricular ejection fraction <40%, number of significantly stenosed coronary arteries, previous coronary revascularization, arterial hypertension, carotid disease, type 2 diabetes mellitus, smoking status, and levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Statistical significance was set at *p* <0.05.

Baseline characteristics of the study population are presented in Table 1. Overall, 101 patients (31.3%) were diagnosed with carotid disease. Patients with concomitant carotid disease had mild to moderate carotid artery stenosis, with 52% (95% confidence interval 46 to 59) occurring in the right carotid artery and 49% (95% confidence interval 43 to 56) occurring in the left carotid artery. Incidences of uncontrolled hypertension and type 2 diabetes mellitus were greater among patients with concomitant carotid disease. Lipid profiles, mean left ventricular ejection fraction, and the distribution of diagnoses at admission were similar in the 2 groups. More patients with carotid disease had 2- or 3-vessel disease on coronary angiography, whereas the rate of 1-vessel disease was higher in those without carotid disease. Accordingly, in patients with carotid disease, the proportion of surgeries for coronary artery bypass grafting was higher (*p* = 0.03) and the proportion of percutaneous coronary interventions was border-

TABLE 3 Medical Therapy During Follow-up				
Medications	All Patients	Carotid Disease		p Value
		+	0	
β Blockers	197 (61%)	55 (55%)	142 (64%)	NS
Angiotensin-converting enzyme inhibitors	165 (51%)	46 (46%)	119 (54%)	NS
Calcium channel blockers	75 (23%)	25 (25%)	50 (23%)	NS
Nitrates	68 (21%)	29 (29%)	39 (18%)	0.02
Statins	209 (65%)	62 (61%)	147 (66%)	NS
Aspirin	228 (71%)	72 (71%)	156 (70%)	NS
Diuretics	81 (25%)	35 (35%)	46 (21%)	0.008

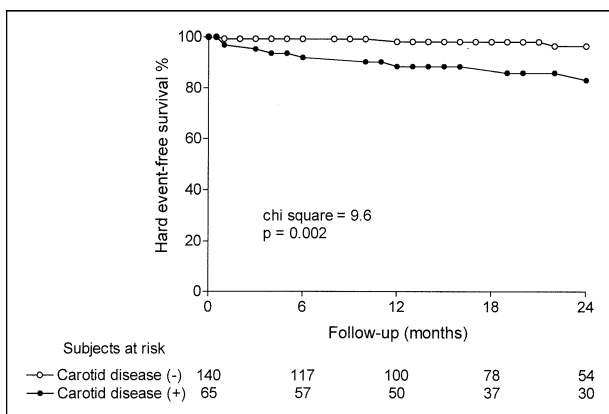


FIGURE 2. Kaplan-Meier survival plot for hard events of invasively treated patients according to presence or absence of carotid disease.

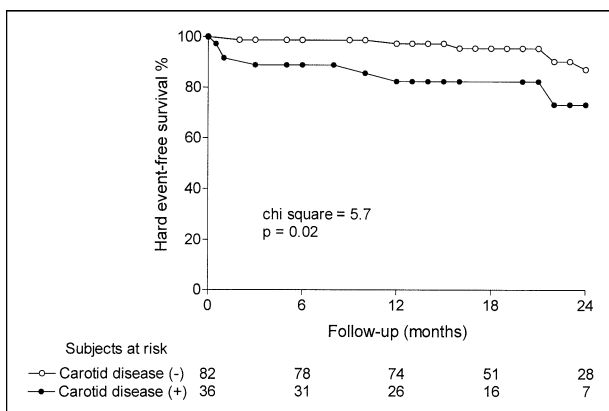


FIGURE 3. Kaplan-Meier survival plot for hard events of conservatively treated patients according to presence or absence of carotid disease.

line lower ($p = 0.07$) than in patients without carotid disease. The proportion of patients treated conservatively was similar in the 2 groups (Figure 1).

No patient was lost to the follow-up of 17 ± 8 months. Seventy-one events were registered: 11 cardiac deaths, 14 myocardial infarctions, 46 recurrences of angina requiring rehospitalization, and 3 noncardiac deaths (1 from stroke and 2 from cancer). We also registered 3 nonfatal strokes, but these were not considered events. During follow-up, patients with carotid disease had significantly higher rates of hard events (Table 2) and recurrent angina requiring rehospitaliza-

tion than did patients without carotid disease. Of those rehospitalized for angina, 8 patients (7.9%) with carotid disease and 6 patients (2.7%) without carotid disease were revascularized ($p = 0.03$). Patients with carotid disease were more likely to be receiving nitrates and diuretics, whereas rates of other prescribed medications were similar (Table 3).

In patients without carotid disease, an invasive strategy resulted in fewer nonfatal myocardial infarctions

($p = 0.02$) during follow-up compared with medical treatment. In patients with carotid disease, no significant differences in outcome related to treatment strategies were found. In conservatively or invasively treated patients, those with carotid disease had a significantly lower event-free survival rate than did those without carotid disease (Table 2 and Figures 2 and 3).

Cox's multivariate regression analysis showed that the presence of carotid disease and left ventricular systolic dysfunction (ejection fraction $<40\%$) were significantly associated with death, rehospitalizations, and hard events. Smoking was a significant predictor of combined events.

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The present study shows that coronary revascularization does not improve outcome in patients with ACS and concomitant carotid disease compared with medical treatment.

Previous studies have demonstrated that extracoronary arterial disease has an independent unfavorable effect on long-term outcome in patients with ACS and chronic CAD.^{1,9,10} Noncoronary arterial disease also has been associated with a higher rate of periprocedural complications and adverse long-term outcomes in patients undergoing coronary artery bypass grafting¹¹ or percutaneous coronary intervention.^{12,13} However, there has been no study on which treatment strategy, conservative or interventional, is better for patients with ACS and concomitant extracoronary burden.

In our study, although patients with carotid disease had greater prevalences of uncontrolled hypertension and type 2 diabetes mellitus and more widespread CAD (according to angiographic data) compared with those without carotid disease, these factors did not appear to be independent predictors of hard events in the multivariate analysis.

Our study underlines the impact of carotid disease on outcome in patients with ACS undergoing different treatment strategies. According to recent large trial results and current guidelines¹⁴⁻¹⁷ in patients with asymptomatic extracranial carotid stenosis and unstable cardiac disease, only medical therapy for carotid disease is recommended. For patients with symptomatic carotid stenosis, endarterectomy is not recommended if the stenosis is mild ($<50\%$). In other cases, the decision should be individualized on the basis of the presence or absence of risk factors for stroke and symptoms. However, patients in previous trials on

carotid disease were not specifically evaluated for the presence of CAD. Hence, their risk may have been underestimated. In all cases, the presence of even mild and asymptomatic carotid disease should serve as a marker of generalized atherosclerosis, and therapy should be aimed at preventing systemic complications such as myocardial infarction and stroke.

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Effect of Sinus Rhythm Restoration on Plasma Brain Natriuretic Peptide in Patients With Atrial Fibrillation

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Plasma brain natriuretic peptide (BNP) was evaluated before and after sinus rhythm restoration in patients with paroxysmal and persistent atrial fibrillation (AF) who had underlying hypertension or coronary heart disease and normal left ventricle function. Twenty-four hours after successful cardioversion, plasma BNP decreased significantly to levels that had been measured in controlled subjects: from 95 to 28 pg/ml in 24 patients in the paroxysmal AF group and from 75 to 41 pg/ml in 36 patients in the persistent AF group. This indicates that AF affects BNP secretion in patients with AF and that some BNP may be atrially delivered. ©2004 by Excerpta Medica, Inc.

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Plasma brain natriuretic peptide (BNP) levels have been used as a marker of left ventricle dysfunction.^{1,2} However, the role of BNP in patients with atrial fibrillation (AF) and normal left ventricular function has not been determined. The present study, limited to patients with normal left ventricle function and AF, was performed to evaluate plasma BNP levels before and after sinus rhythm restoration in consecutive patients with paroxysmal and persistent AF, who were referred for electrical cardioversion.

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Patients with paroxysmal or persistent AF due to either well-controlled mild or moderate hypertension or stable coronary heart disease, or lone AF, were enrolled prospectively. Patient inclusion criteria were (1) paroxysmal AF lasting <48 hours; (2) persistent AF (lasting for >48 hours within a 24-month period); (3) normal left ventricular function (ejection fraction ≥50%); and (4) absence of clinical heart failure and referred for electrical cardioversion. All patients were optimally treated for hypertension or coronary heart